CELANESE

March 2, 1983
GAR-103-83

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Document Control Officer
Office of Toxic Substances (WH-557)
Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Sir:

We are submitting to you for your information a Formaldehyde Clearinghouse Data Form, together with cover letter dated January 6, 1983, submitted to Dr. W.F. McCallum of the National Center for Toxicological Research by Dr. R. Kroes, Director, CIVO Institutes TNO, for consideration by the NCTR Workshop. The Clearinghouse Form and cover letter give a summary of a rat inhalation study of acetaldehyde which is currently in progress. We are attempting to obtain further information on this study from the investigators, and will forward it to you as soon as it is available.

Sincerely yours,

George A. Rodenhausen
Director
Environmental, Health
and Safety Affairs

GAR:js
att.

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date 6 January 1983
our ref 6681 KR/CBJ
your ref
subject

Dear Dr. McCallum,

Many thanks indeed for your letter of December 1982 concerning the Consensus Workshop on Formaldehyde.

I would like to submit the following three questions, ranked by preference:

1. What role does the cytotoxicity of formaldehyde play in its carcinogenicity?

   Chemical carcinogens can be divided into complete and incomplete carcinogens. Complete carcinogens are capable of both initiating and promoting the process of carcinogenesis; they can induce cancer by themself. An incomplete carcinog can act either as an initiator or as a promotor; an initiator needs a promot and a promotor needs an initiator to be able to act as a complete carcinogen or in other words, to be able to induce cancer.

   Formaldehyde (and possibly also acetaldehyde) is a genotoxic agent and therefore, possesses initiating activity. Its strong cytotoxicity (which may lead to cell damage followed by regenerative hyperplasia) is most probably responsible for its promoting activity. Since formaldehyde only or preferably reac with single strand DNA and the incidence of dividing cells in the normal intact nasal epithelium is low, it is obvious to assume that the initiating potential of formaldehyde in concentrations not resulting in cell damage is extremely low. On the other hand, concentrations of formaldehyde leading to cell damage followed by cell proliferation (and the presence of much single-stranded DNA) may be very effective with respect to initiation. Moreover, the increased cell turnover may strongly enhance the fixation of relevant DNA damage, and subsequently may clearly increase the chance of progression of pre-cancer cells to cancer.

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As a consequence formaldehyde (and possible also acetaldehyde in concentrations that do not induce tissue damage, seems to be a very weak initiator (only a few dividing cells are available) without promoting activity (there is no increased cell turnover). This means that in such sub-cytotoxic concentrations formaldehyde cannot act as a complete carcinogen, but only as a very weak initiator, and consequently cannot induce cancer by itself. However, recurrent tissue damage followed by cell proliferation due to another factor might create the appropriate conditions under which exposure to sub-cytotoxic levels of formaldehyde means a real carcinogenic risk.

The following sub-questions related to the role of the cytotoxicity can be posed:

a. Should exposure to sub-cytotoxic concentrations of formaldehyde be considered a carcinogenic risk?

b. Should exposure to sub-cytotoxic levels of formaldehyde under conditions of recurrent tissue damage followed by cell proliferation due to another factor be considered a carcinogenic risk?

To answer these questions studies sponsored by the Dutch Cancer Foundation will be started in our Institute in 1983. More information on these studies is given ./. in DATA FORM 1 (enclosed).

2. What is known about the carcinogenicity of acetaldehyde, which is a compound chemically closely comparable to formaldehyde?

Acetaldehyde is used in the manufacture of synthetic chemicals, as well as for solvent purposes in the rubber, tanning and paper industries. Another source of human exposure to acetaldehyde is cigarette smoke, which has been found to contain acetaldehyde levels up to 2000 ppm.

Long-term inhalation studies with acetaldehyde in Syrian golden hamsters carried out in our Institute have shown that malignant nasal and laryngeal tumors occurred at an exposure level of 2500-1650 ppm (the initial level of 2500 ppm was reduced several times to avoid severe growth retardation and early mortality) but not at an exposure level of 1500 ppm. At both levels severe degeneration, inflammation, hyperplasia and metaplasia were found in the nasal mucosa. To verify these findings in hamsters, short- and long-term inhalation studies with acetaldehyde in rats have been initiated in our Institute. The short-term studies revealed severe degenerative, hyperplastic and metaplastic epithelial changes in the nose at levels of 1000, 2200 and 5000 ppm; similar changes were also found in the larynx at the two highest exposure levels. The long-term study with a serial killing design and using 750,1500 and 3000 ppm acetaldehyde as exposure levels had been running for 21 months in January 1983.

The histopathological examination of rats killed after 3, 6 or 12 months revealed hyper- and metaplastic epithelium with massive keratinisation in the nose, and similar, but less severe changes in the larynx at the highest exposure level Less severe degenerative and hyper/metaplastic changes in the nose were also found at the lower exposure levels. The first nasal carcinoma (a squamous cell carcinoma from the respiratory epithelium) was found in a high dose rat in week 44; after an exposure period of 15 months a considerable number of high dose rats were found to have a nasal carcinoma (both squamous cell carcinomas of the respiratory epithelium and adenocarcinomas of the olfactory epithelium occurred); in addition, a few lower dose rats had already developed a nasal carcinoma.

Only a few genotoxicity tests with acetaldehyde have been reported; the compound appeared to be capable of inducing crosslinks between DNA strands and SCE's in human lymphocytes and ovary cells of Chinese hamsters. Acetaldehyde is negative in the Ames test.

The above findings with acetaldehyde seem to put the results obtained with formaldehyde in a wider perspective. Studies aimed at elucidating the role of the cytotoxicity in the carcinogenicity of both compounds are urgently needed. Such studies do not seem to be relevant only for an insight into the mode of action of these two chemicals, but they might well serve a more general purpose, namely getting a better insight into the significance of respiratory tract irritants (cytotoxins) for the local induction of tumours. Obvious examples of such irritants other than formaldehyde and acetaldehyde are acrolein and furfural.

3. Is exposure to formaldehyde (and acetaldehyde) a risk factor for the development of larynx and lung cancer in man?

In contrast to humans, rats, mice and hamsters are obligate nose breathers. Thus, the site of formaldehyde (and acetaldehyde) carcinogenicity may be the larynx and the lungs in humans.

Formaldehyde and acetaldehyde occur in the vapour phase of cigarette smoke at relatively high levels (formaldehyde up to 30 ppm and acetaldehyde up to 2000 ppm), thus, a smoker who actively inhales the smoke may expose his larynx, bronchi and lungs to relatively high concentrations of these aldehydes. To the best of our knowledge, there are no adequate epidemiological studies which address this problem, although occupational and environmental exposure to these aldehydes is prevalent, and many people still smoke tobacco.

6681 KR/CBJ
6 January 1983

I would like to nominate Dr. V.J. Feron of our Institute as a member of the Workshop Committee.
Dr. Feron (pathologist/toxicologist) is head of the department of Biological Toxicology and an expert in the field of toxicity and carcinogenicity testing of aldehydes, such as acetaldehyde, acrolein and furfural.
The aforementioned studies on acetaldehyde were carried out by or under the direct supervision of Dr. Feron. A research programme on the significance of the cytotoxicity of formaldehyde for its carcinogenicity has just been started (January 1983) and will be conducted by Dr. Feron; this research is sponsored by the Dutch Cancer Foundation.
Dr. Feron also served on the Special Advisory Committee on Formaldehyde, a committee, set up by the Dutch Ministry of Public Health and Environmental Hygiene. Recently an advice on "Formaldehyde and Cancer in Humans" appeared. The advice is written in Dutch, but an informal English translation exists, and is enclosed.

I have further enclosed two DATA FORMS concerning the Formaldehyde Clearinghouse; one deals with a project on the significance of the cytotoxicity of formaldehyde and other aldehydes for the carcinogenic effect of such compounds on the respiratory tract, and the other concerns a lifespan inhalation carcinogenicity study of acetaldehyde in rats.

Finally I would like to congratulate the Environmental Protection Agency and the National Center for Toxicological Research for their fine and important initiativ Sincerely I hope that Dr. Feron, one of my best collaborators, will be selected as a participant.

Yours sincerely,

INSTITUTE CIVO
TOXICOLOGY AND NUTRITION TNO

Robert Kroes

Dr. R. Kroes, director.

Encls.

FORMALDEHYDE CLEARINGHOUSE

DATA FORM

II

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

Jefferson, Arkansas

OMB 0910-0148
Expires 12/31/83

INSTRUCTIONS FOR COMPLETING NCTR/EPA FORMALDEHYDE CLEARINGHOUSE DATA FORM

- Chemical Name and CAS Registry Number: Please complete separate form for each chemical being tested.
- Purity/Form: Self-explanatory.
- Title of Project: Title should indicate clearly and briefly the scope of the project.
- Start and End Dates: Self-explanatory; estimate if necessary.
- Projected Date for Data Availability: Self-explanatory.
- Principal Investigators: Names should appear in the following order: last, first, middle initial and title.
- Address: Name, street, city, state and ZIP code of performing organization should be listed. Indicate country if project is not performed in the United States.
- Sponsoring Organization(s): Name and address of any sponsoring organizations, including principal contact person, should be entered here.
- Type of Toxicological Testing: Check the box(es) which most clearly describes the kind of testing being done. Chemical disposition studies include metabolism, uptake, distribution and elimination. Human case histories may be included under "Epidemiology." Under the heading "Other," please identify the type of testing being done. This may include such testing as neurotoxicity and specific organ toxicity as well as chemical fate and transport, chemical and physical characteristics, and industrial hygiene studies.
- Summary of Work: Include information on test species/strain, source and lot number of compound (if available), purity of compound, dose levels, route(s) of administration, vehicle/carrier, and duration of exposure.
- Key Words: Please designate key words you wish to have associated with the project.
- Publications: List all publications produced by your group which relate to this project or describe previous work done by you in this specific area. Please provide, if possible, reprints of these publications and preprints of accepted manuscripts.

Return form and publications to:

William F. McCallum, D.V.M., Coordinator, HFT-100
NCTR/EPA Clearinghouse on Formaldehyde
National Center for Toxicological Research
Jefferson, Arkansas 72079
U.S.A.

NCTR/EPA CLEARINGHOUSE ON FORMALDEHYDE

Chemical Name	CAS Registry Number (for related compounds)
Acetaldehyde, C_2H_4O	75-07-0

Purity/Form

P.A.; vapour exposure

Title of Project

Lifespan inhalation carcinogenicity study of acetaldehyde in rats

Start Date	End Date	Projected Date for Data Availability
March 1981	March-July 1984	Interim results: March 1983 Final report : July 1984

Principal Investigators

Feron, V.J., Dr; Appelman, L.M., Drs; Woutersen, R.A., Dr.

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Sponsoring Organization(s) 1. Ministry of Health and Environment, Dr. Reijersstraat 12, Leidschendam, The Netherlands (Drs. A.W. van der Wielen); 2. Koningin Wilhelmina Fonds (Netherlands Cancer Foundation), Sophialaan 8-10, 1075 BR Amsterdam (Drs. H.W. Waaijers) 3. Institute CIVO-Toxicology and Nutrition TNO (see above), Dr. R. Kroes

Cooperating Organization(s)

National Institute of Public Health, Bilthoven, The Netherlands (Drs. C.A. van der Heijde

Types of Toxicological Testing (check applicable boxes)

- ☐ Chemical Disposition/Kinetics
- ☐ Biochemistry
- ☐ Acute Toxicity
- ☐ Genotoxicity/Mutagenicity
- ☐ Reproductive Toxicity/Teratology
- ☐ Behavioral Toxicity
- ☐ Immune Toxicity
- ☒ Chronic Toxicity
- ☒ Carcinogenicity
- ☐ Epidemiology
- ☐ Environmental Occurrence
- ☐ Risk Estimation
- ☒ Other sub acute toxicity

OMB 0910-0148
Expires 12/31/83

Summary of Project (250 words or less)

A lifespan inhalation carcinogenicity study of acetaldehyde is carried out in rats. Four groups of rats are used, each consisting of 105 males and 105 females. The dose-levels are 0, 750, 1500 and 3000 ppm. Interim kills are after 3, 6 and 12 months; "recovery" groups are included.

This study had been running for 21 months in January 1983. After 3, 6 and 12 months hyper- and metaplastic epithelium with massive keratinisation was found in the nose, and similar but less severe changes in the larynx at the highest exposure level. Less severe degenerative and hyper/metaplastic changes in the nose were also seen at the lower exposure levels. Already after an exposure period of 15 months a considera number of high-dose rats were found to have a nasal carcinoma; both squamous cell carcinomas of the respiratory epithelium and adenocarcinomas of the olfactory epitheliu occurred.

Key Words

Acetaldehyde, carcinogenicity, rat, nasal carcinomas.

Publications (list separately)

- See the list attached
- In addition to these studies on acetaldehyde several studies on <u>acrolein</u> and <u>furfural</u> have been carried out in our laboratory, and have been published too.

LIST OF PUBLICATIONS

1. Kruysse, A., V.J. Feron and H.P. Til
Repeated exposure to acetaldehyde vapor. Studies in Syrian golden hamsters.
Arch. Environ. Health 31 (1975) 449-452

2. Feron, V.J.
Effects of exposure to acetaldehyde in Syrian hamsters simultaneously treated with benzo(a)pyrene or diethylnitrosamine.
Progr. Exp. Tumour Res., 24 (1979) 162-176

3. Feron, V.J., A. Kruysse and R.A. Woutersen
Respiratory tract tumours in hamsters exposed to acetaldehyde vapour alone or simultaneously to benzo(a)pyrene or diethylnitrosamine
Eur. J. Cancer Clin. Oncol. 18 (1982) 13-31

4. Appelman, L.M., R.A. Woutersen and V.J. Feron
Inhalation toxicity of acetaldehyde in rats.
I Acute and sub-acute studies.
Toxicology 23 (1982) 293-307